Travelling Waves of Cell Dierentiation

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Abstract. The paper is devoted to modelling of cell differentiation in an initially homogeneous cell population. The mechanism which provides coexistence of two cell lineages in the initially homogeneous cell population is suggested. If cell differentiation is initiated locally in space in the population of undifferentiated cells, it can propagate as a travelling wave converting undifferentiated cells into differentiated ones. We suggest a model of this process which takes into account intracellular regulation, extracellular regulation and different cell types. They include undifferentiated cells and two types of differentiated cells. When a cell differentiates, its choice between two types of differentiated cells is determined by the concentrations of intracellular proteins. Differentiated cells can either stimulate differentiation into their own cell lineage or into another cell lineage. In the case of the positive feedback, only one lineage of differentiated cells will finally appear. In the case of negative feedback, both of them can coexist. In this case a periodic spatial pattern emerges behind the wave.

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1 Multi-scale models of cell population dynamics

1.1 Multi-scale models

In this work we study a multi-scale model of cell differentiation. Cell differentiation occurs in many physiological processes in normal and pathological situations. In some cases, cell differentiation propagates in space as a travelling wave. It provides transition of the tissue from one state to another one. Such phenomena occur in various inflammatory diseases, tumor growth, in other spreading diseases (Volpert 2014). Existence of such waves, their structure and speed of propagation are interesting from the biological and from the modelling points of view.

Multi-scale models in biology actively develop in order to describe physiological processes. There are various approaches to multi-scale modelling and numerous applications (see Anderson et al. 2007; Bernard 2013; Cristini and Lowengrub 2010; Osborne et al. 2010; Volpert

2014, and the references therein). Cell populations in multi-scale models can be described by discrete or continuous methods. Among them cellular automata, lattice Boltzmann method and various particles methods (Anderson et al. 2007, Deutsch and Dormann 2005; Karttunen et al. 2004; Patel et al. 2001; Satoh 2011; Trofimov 2003). These approaches allow a detailed description of cell behavior, cell-cell interaction and other aspects of complex biological media. On the other hand, they are applicable for a relatively small number of cells and they do not admit analytical investigation. Continuous models are represented by ordinary and partial differential equations for cell concentrations. In particular, these can be reaction-diffusion equations which take into account random cells motion and their birth and death; Navier-Stokes equations and Darcy equations describe convective motion of the medium.

Multi-scale models include intracellular and extracellular regulations of biological cells. Intracellular regulation is particularly important because it determines the cell fate, that is the choice between its self-renewal, differentiation and apoptosis. It can be described by ordinary differential equations for intracellular concentrations, by Boolean approach or by probabilistic methods if a small number of molecules participate in this regulation and their concentrations cannot be considered.

Extracellular regulation can be effectuated by various local mechanisms in the given tissue (growth factors, cytokines) or by means of global control from other organs and tissues through endocrine signaling. Extracellular substances diffuse in the tissue and influence intracellular regulation of cells. Distribution of these substances can be described by reaction-diffusion equations.

Cell populations, intracellular and extracellular regulations can be modelled with hybrid discrete-continuous methods. They describe cells as individual objects with various lattice or off-lattice methods, intracellular regulatory networks with ordinary differential equations and extracellular substances with partial differential equations. Such models are developed in order to study hematopoiesis (Bessonov, Eymard et al. 2012; Demin et al. 2010; Kurbatova et al. 2011; Kurbatova et al. 2013). and other physiological processes (Glade and Stephanou 2013). They can take into account cell motion, division, death, their interaction with each other and with the surrounding medium. Transition from hybrid to continuous models can be justified for some model examples (Bessonov, Kurbatova et al. 2012).

Multi-scale models can manifest interesting nonlinear dynamics different in comparison with conventional reaction-diffusion equations. In this work we will study propagation of reaction-diffusion waves for a multi-scale model presented in the next section.

1.2 Models with unmovable cells

Let us consider a cell population which fills some spatial domain. We will consider here one-dimensional problems. Each space point corresponds either to one cell or to a number of cells which satisfy some conditions formulated below. We will denote cell types by $A_1, ..., A_n$ and their concentrations by $c_1(x,t), ..., c_n(x,t)$. We will make the following assumptions:

1. Each cell has a fixed spatial location which does not change in time. Let us recall that

cells can have some specific intrinsic mechanism of motion or they can move due to some forces exerted from the other cells or from the surrounding medium. Therefore we suppose that these both driving forces of cell motion are absent. The absence of convective motion implies that the total cell concentration c_0,

$$c_0 = c_1(x,t) + ... + c_n(x,t)$$

is constant. Otherwise a nonuniform concentration distribution will result in pressure gradients and the motion of the medium,

2. Cells of the same type which belong to the same space point are identical in the sense that they have the same values of intracellular variables. Distribution of intracellular variables inside each cell is uniform.

Let $p^1, ..., p^n$ be intracellular variables corresponding to cells $A_1, ..., A_n$. Each of the variables p^i, $i = 1, ..., n$ can be a vector. Since cells do not move and since they are identical at each space point, then intracellular variables can be considered as functions of x and of t. We will describe their evolution inside each cell by ordinary differential equations:

$$\frac{\partial p^i}{\partial t} = F^i, \quad i = 1, ..., n, \tag{1.1}$$

where F^i is the rate of their production or consumption. We write here partial derivative since these functions can depend on x. If intracellular substances can be transported between neighbouring cells by gap junctions, then instead of equation (1.1) we can consider the corresponding reaction-diffusion equation.

Next, we introduce extracellular variables $u_1, ..., u_m$ which can be produced or consumed by cells of the given tissue or they can come from other tissues. They can also diffuse in the tissue. We describe them by reaction-diffusion equations

$$\frac{\partial u_j}{\partial t} = D_j \frac{\partial^2 u_j}{\partial x^2} + G_j, \quad j = 1, ..., m, \tag{1.2}$$

where G_j is the rate of their production or consumption.

Finally, though the total concentration c_0 is supposed to be constant, individual concentrations $c_1, ...c_n$ can change. This means that cells can change their type but their total number at each space point does not change. Therefore, cells can differentiate but they cannot self-renew or die.

We need to specify conditions of cell differentiation. Since it is determined by the intracellular regulation, cells A_i can change to A_j if the vector of intracellular concentrations $p^i(x,t)$ takes some given critical value p_c^{ij}. In this case, the variables c_i are discontinuous. Cell concentrations can also be described by ordinary differential equations

$$\frac{\partial c_i}{\partial t} = H_i, \quad i = 1, ..., n, \tag{1.3}$$

where H_i is the rate of their production or disappearance which depend on the intracellular and extracellular variables.

Thus, we have a closed system of equations (1.1)-(1.3) for cell concentrations, intracellular and extracellular variables. Functions F^i, G_J and H_i depend on p^i, u_j and c_i. Let us note that numerical discretization of this model with a finite cell size can be considered as a hybrid model. Hence continuous and hybrid models are closely related in this formulation. In the next section we will consider an analytical example. Section 3 is devoted to the results of numerical simulations of some model problems.

1.3 Reaction-diffusion waves in physiology

The theory of reaction-diffusion waves develops under the influence of various applications (see Volpert et al. 1994; Volpert 2014, and the references therein). Reaction-diffusion waves in physiology describe various transition processes. If we consider a tissue and initiate some cell transformation (differentiation, proliferation, apoptosis), then it can propagate in space converting the tissue from one state to another one. In particular, various spreading diseases including tumor growth (Bessonov et al. 2009; Volpert 2014) and atherosclerosis (El Khatib et al. 2007, 2009, 2012) develop by this mechanism. Travelling waves of cell differentiation are studied in (Trewenack and Landman 2009).

The mechanism of wave propagation in biological tissues is based on the interaction of intracellular and extracellular regulations. We will consider bistable kinetics of the intracellular regulation of undifferentiated cells. Each of the stable stationary points corresponds to differentiation into one of two types of differentiated cells. Differentiated cells produce some substances which diffuse in the extracellular matrix and influence intracellular kinetics of other undifferentiated cells. They can promote differentiation into the same cell type or into the other cell type. We will see that in the second case, two types of differentiated cells can coexist forming a periodic pattern behind the wave. This periodic in space structure does not appear as a result of instability of a homogeneous in space solution but as a global bifurcation.

2 Analytical example

We consider a cell population located along the real line. There are two cell types, A and B. Cells of the type A can differentiate in the cells of the type B. Cells of the type A contain an intracellular protein with the concentration p. When it reaches a critical value p_*, the cell changes its type. The cells of the type B produce a growth factor u which can diffuse in the extracellular matrix. It can influence production of the protein p. We will assume that cells do not move. Then p can be considered as a function of the space variable x and of time t. Hence we obtain the following system of equations:

$$\frac{\partial u}{\partial t} = d\,\frac{\partial^2 u}{\partial x^2} + W_1 - \sigma u, \tag{2.1}$$

$$\frac{\partial p}{\partial t} = W_2, \tag{2.2}$$

where W_1 and W_2 are the rates of production of the corresponding substances.

Suppose that cells of the type A fill the half-line $x < \xi(t)$ and cells of the type B the half-line $x > \xi(t)$. We will look for a travelling wave solution for which the coordinate $\xi(t)$ moves with a constant speed, $\xi = st$. Let us note that $s < 0$. In the moving coordinates, and keeping for convenience the same notations for the concentrations, we obtain the following system of equations:

$$du'' + su' + W_1 - \sigma u = 0, \tag{2.3}$$

$$sp' + W_2 = 0. \tag{2.4}$$

Here prime denotes differentiation with respect to the independent variable $z = x - st$. We can assume that cells A are located for $z < 0$ and cells B for $z > 0$. Then $p < p_*$ for $z < 0$. Set

$$W_1 = k_1, \quad W_2 = k_2 u.$$

This means that cells B produce the substance u with a constant rate, and the rate of production of p is a linear function of u.

We solve system (2.3), (2.4). From equation (2.4) we get:

$$u(x) = u_* e^{\lambda_1 z}\ , \quad z < 0, \qquad u(x) = \frac{k_1}{\sigma} + \left(u_* - \frac{k_1}{\sigma}\right) e^{\lambda_2 z}\ , \quad z > 0.$$

Here $u(0) = u_*$,

$$\lambda_1 = -\frac{s}{2} + \sqrt{\frac{s^2}{4} + \sigma}\ > 0, \qquad \lambda_2 = -\frac{s}{2} - \sqrt{\frac{s^2}{4} + \sigma}\ < 0.$$

From continuity of the solution and its first derivative,

$$u(-0) = u(+0), \qquad u'(-0) = u'(+0),$$

we obtain the equality

$$u_* \lambda_1 = \left(u_* - \frac{k_1}{\sigma}\right) \lambda_2,$$

which allows us to express u_*:

$$u_* = \frac{k_1 \lambda_2}{\sigma(\lambda_2 - \lambda_1)}\ . \tag{2.5}$$

Integrating equation (2.4) from $-\infty$ to 0 and taking into account (2.5), we obtain:

$$s = -\frac{u_* k_2}{p_* \lambda_1}\ = -\frac{k_1 k_2 \lambda_2}{p_* \sigma \lambda_1 (\lambda_2 - \lambda_1)}\ .$$

We can write this relation in another form:

$$s = \frac{k_1 k_2}{p_* \lambda_1^2 (\lambda_2 - \lambda_1)} \quad (s < 0). \tag{2.6}$$

It is an equation with respect to c. Its right-hand side is a decreasing function of c equal 0 at $-\infty$ and negative for $s = 0$. Therefore equation (2.6) has a unique solution.

This example shows the existence of waves of cell differentiation. We calculate the speed of wave propagation. In a more complex model of lineage choice (Section 3) existence of waves and their structure will be studied numerically.

3 Lineage choice

In this section we consider the problem of lineage choice where undifferentiated cells differentiate into one of two types of differentiated cells. There are three cell types, undifferentiated cells A, differentiated cells B_1 and B_2. Cells A contain two intracellular proteins, p_1 and p_2. Their concentrations are described by ordinary differential equations:

$$\frac{dp_1}{dt} = F_1(p_1, p_2) + b_{11}u_1 + b_{12}u_2, \tag{3.1}$$

$$\frac{dp_2}{dt} = F_2(p_1, p_2) + b_{21}u_1 + b_{22}u_2. \tag{3.2}$$

The functions F_1 and F_2 will be specified below. Extracellular concentration u_1 is produced by differentiated cells B_1, and u_2 is produced by cells B_2. Concentrations u_1 and u_2 are described by the equations

$$\frac{\partial u_1}{\partial t} = d_1 \frac{\partial^2 u_1}{\partial x^2} + W_1, \tag{3.3}$$

$$\frac{\partial u_2}{\partial t} = d_2 \frac{\partial^2 u_2}{\partial x^2} + W_2. \tag{3.4}$$

Cells of the type A are located at $x > \xi(t)$, cells B_1 and/or B_2 at $x < \xi(t)$. The value $\xi(t)$ increases in time, that is the wave speed is positive.

If the intracellular concentration p_1 is greater than a critical value, $p_1 \geq p_1^*$, then the cell A changes its type to B_1, if $p_2 \geq p_2^*$, then it changes its type to B_2. Once a cell is differentiated, it cannot change any more.

We introduce the concentration c_A of cells A, the concentration c_1 of cells B_1 and the concentration c_2 of cells B_2. At each space point x these three concentrations can have only two values, 0 or 1. Consider some interval filled by cells A. Therefore, in this interval $c_A = 1$, $c_1 = c_2 = 0$. If at some point x of this interval p_1 becomes greater than p_1^*, then the cell A changes type to B_1. Hence, for this x, $c_A = 0$, $c_1 = 1$, $c_2 = 0$. Similarly, if p_2 becomes greater than p_2^*, then $c_A = 0$, $c_1 = 0$, $c_2 = 1$.

We set

$$W_1 = k_1 c_1, \quad W_2 = k_2 c_2.$$

This means that cells B_1 produce u_1, cells B_2 produce u_2. The rates of production vanish if the concentrations of the corresponding cells equal zero.

In the remaining part of this section we present the results of numerical simulations of the model described above. We use an implicit finite difference scheme with Thomas algorithm.

3.1 Bistable kinetics

In order to study lineage choice, we introduce intracellular regulation with bistable kinetics. We set

$$F_1(p_1, p_2) = k_1 p_1 (1 - a_{11} p_1 - a_{12} p_2), \quad F_2(p_1, p_2) = k_2 p_2 (1 - a_{21} p_1 - a_{22} p_2). \tag{3.5}$$

If the extracellular variables vanish, $u_1 = u_2 = 0$, then system (3.1), (3.2) is a closed system of two ordinary differential equations for the intracellular variables p_1, p_2. It has four stationary points, $P_0 = (0, 0)$, $P_1 = (1/a_{11}, 0)$, $P_2 = (0, 1/a_{22})$ and $P_3 = (p_1^0, p_2^0)$, where p_1^0 and p_2^0 is a solution of the system

$$a_{11} p_1 + a_{12} p_2 = 1, \quad a_{21} p_1 + a_{22} p_2 = 1.$$

We will suppose that it has a positive solution. The point P_0 is always unstable, the points P_1 and P_2 are stable and P_3 is unstable if $a_{21} > a_{11}, a_{21} > a_{22}$. The point P_3 is stable if these inequalities are opposite. In this case P_1 and P_2 are unstable.

Let us consider the case where the points P_1 and P_2 are stable. If the initial condition of this system belongs to the basin of attraction of one of them, then the trajectory approaches this stationary point. If it is P_1, then the value p_1 will reach the critical value p_1^* and the cell will differentiate into cell B_1. If the trajectory approaches the stationary point P_2, then the value p_2 will reach the critical value p_2^*, and the cell will differentiate into cell B_2. These cells will produce extracellular substances u_1 or u_2 which will diffuse in the extracellular matrix and influence intracellular regulation of other cells.

Figure 1 (left) shows the results of numerical simulations of this model with the following values of parameters: $a_{11} = a_{22} = 0.5, a_{12} = a_{21} = 1, b_{11} = b_{22} = 0.1, b_{12} = b_{21} = 0$, $D_1 = D_2 = 0.1, k_1 = k_2 = 0.1, p_1^* = p_2^* = 1.5$. This is the basic set of parameters. In what follows we will only indicate the values which are modified in comparison with these ones. The initial condition is $p_1 = 0.5$ in the interval $0 < x < 1$ and $p_1 = 0$ in the remaining part of the interval. The length of the interval $L = 100$. All other variables are also set zero. Let us note that we introduce a new notation c for cell concentrations. We put $c = 0$ if $c_A = 1, c_1 = 0, c_2 = 0$, $c = 1$ if $c_A = 0, c_1 = 1 c_2 = 0$ and $c = 2$ if $c_A = 0, c_1 = 0, c_2 = 1$.

Due to the choice of initial condition, the intracellular variable p_1 grows and approaches its value at the stationary point P_1. When it reaches the critical value p_1^*, the cell differentiates into cell B_1. Cells B_1 produce the extracellular substance u_1 which diffuses along the

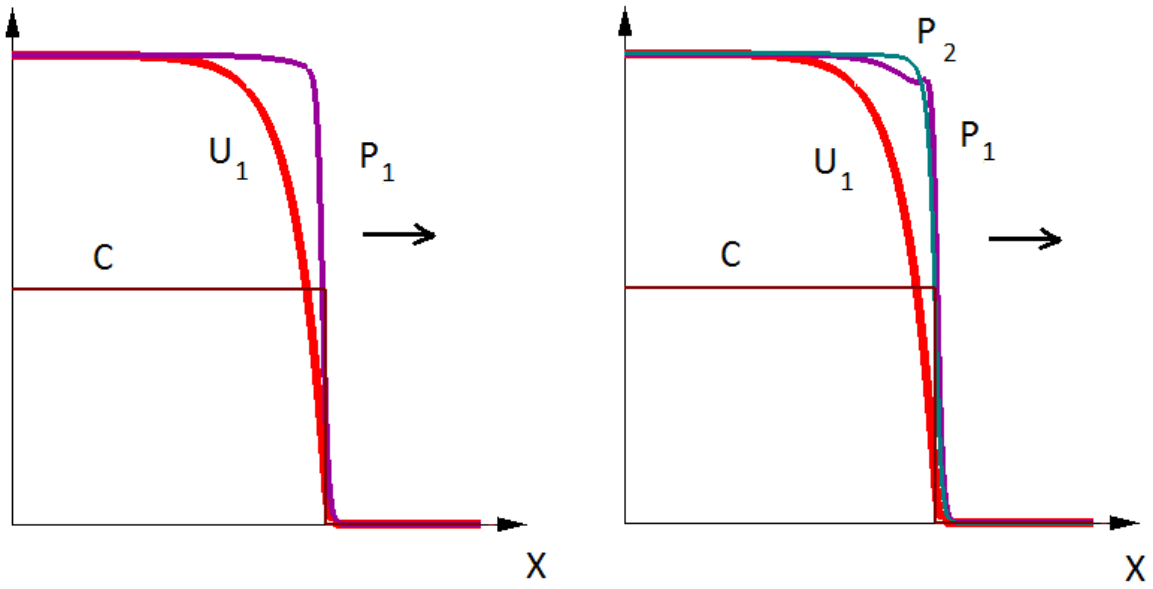

Figure 1: Snapshot of solution. The curves show the values of the corresponding concentrations as functions of the space variable x. Undifferentiated cells A differentiate into cells B_1. They produce extracellular substance u_1. It stimulates production of the intracellular substance p_1. When it reached the critical value p_1^*, the cell differentiate. Differentiated cells gradually fill the whole interval. Left: points P_1 and P_2 are stable, concentration p_2 in the intracellular regulation remains zero. Right: point P_3 is stable. Both concentrations p_1 and p_2 converge to some positive values. However cells A differentiate only in cells B_1. The value $c = 1$ corresponds to $c_A = 0, c_1 = 1, c_2 = 0$ and $c = 0$ to $c_A = 1, c_1 = 0, c_2 = 0$ (see the explanation in the text).

interval and stimulates further production of the intracellular variable p_1. Hence we observe a travelling wave of differentiation of cells A into cells B_1.

Since the initial concentration p_2 equals zero, it remains zero, and the model is reduced to a single intracellular equation and a single extracellular equation (cf. Section 2). For other choice of initial conditions and parameters, two types of differentiate cells can be present in the beginning. However one of the two cell lineages will dominate another one and will expand on the whole interval. Therefore undifferentiated cells will differentiate only in one cell lineage. Two cell lineages cannot coexist in this model.

This conclusion remains true even in the case where the point P_3 is stable. The intracellular concentrations p_1 and p_2 will converge to this stationary points. If the critical values p_1^* and p_2^* are less than the values at this stationary point, then cells will differentiate. Depending on which of the critical values is reached first, the cell will differentiate into B_1 or B_2. As before, only one cell lineage is obtained. Figure 1 (right) shows the distributions of intracellular variables p_1 and p_2 for the values of parameters $a_{11} = a_{22} = 1, a_{12} = a_{21} = 0.5$,

$b_{12} = 0.1, b_{21} = 0.05$. Though p_2 grows and reaches the same final value as p_2^*, it reaches its critical value after p_1. Therefore cells differentiate only into cells B_1.

3.2 Stable undifferentiated state

In this section we consider the intracellular kinetic functions in the form

$$F_1(p_1, p_2) = k_1 p_1^2(1 - a_{11}p_1 - a_{12}p_2) - s_1 p_1, \quad F_2(p_1, p_2) = k_2 p_2^2(1 - a_{21}p_1 - a_{22}p_2) - s_2 p_2. \quad (3.6)$$

The difference in comparison with the functions (3.5) is that the reaction rates are proportional to the second power of the concentrations. The stationary points of the corresponding system

$$\frac{dp_1}{dt} = F_1(p_1, p_2), \quad \frac{dp_2}{dt} = F_2(p_1, p_2) \quad (3.7)$$

are as follows: $P_0 = (0, 0)$, $P_{10} = (p_1^{(1)}, 0)$, $P_{20} = (p_1^{(2)}, 0)$, where $p_1^{(1)}$ and $p_1^{(2)}$ are solutions of the equation

$$p_1(1 - a_{11}p_1) = \frac{s_1}{k_1},$$

$P_{01} = (0, p_2^{(1)})$, $P_{02} = (0, p_2^{(2)})$, where $p_2^{(1)}$ and $p_2^{(2)}$ are solutions of the equation

$$p_2(1 - a_{22}p_2) = \frac{s_2}{k_2},$$

and also up to four stationary points with positive coordinates which can be found as solutions of the system of equations

$$p_2 = \frac{1 - a_{11}p_1}{a_{12}} - \frac{s_1}{a_{12}k_1}\,\frac{1}{p_1}, \quad p_1 = \frac{1 - a_{22}p_2}{a_{21}} - \frac{s_2}{a_{21}k_2}\,\frac{1}{p_2}.$$

It can have from zero to four positive solutions depending on the values of parameters.

It can be easily verified that the point P_0 is stable. Indeed, the corresponding matrix has negative eigenvalues. Let $0 < p_1^{(1)} < p_1^{(2)}$ and $0 < p_2^{(1)} < p_2^{(2)}$. Then the points P_{20} and P_{02} are also stable. In the case where there are four stationary points with positive coordinates, one of them is stable.

There are two different patterns of solutions depending on parameters b_{ij}. Let us consider two specific examples. If $b_{11}, b_{22} > 0$ and $b_{12} = b_{21} = 0$, then the substances $u_i, i = 1, 2$ produced by cells B_i stimulate production of intracellular substances p_i. In their turn, they lead to differentiation of cells A into cells B_i. Therefore we observe here a positive feedback between intracellular regulation, extracellular regulation and cell differentiation. In this case, behavior of the system is qualitatively similar to that described in the previous section. One of the cell lineages B_1 or B_2 dominates another one. It expands on the whole space interval. All cells differentiate into only one cell lineage.

In the second example, $b_{11} = b_{22} = 0$ and $b_{12}, b_{21} > 0$. This means that the substance u_1 produced by cells B_1 stimulate production of the intracellular substance p_2, while u_2 stimulates production of p_1. Hence there is a negative feedback, and cells B_1 upregulate production of B_2, while cells B_2 promote productions of cells B_1. Behavior of the system is qualitatively different in this case compared with the previous one. Both types of differentiated cells can be obtained here.

Figure 2 shows propagation of the wave of cell differentiation for the case $b_{11} = b_{22} = 0$ and $b_{12} = b_{21} = 0.1$ (the values of other parameters are given in Section 3.1). The distribution of the concentration of cells c behind the wave represents a periodic patterns with the values $c = 1$ (cells B_1) and $c = 2$ (cells B_2). Distributions of p_1 and p_2, u_1 and u_2 have also space oscillations.

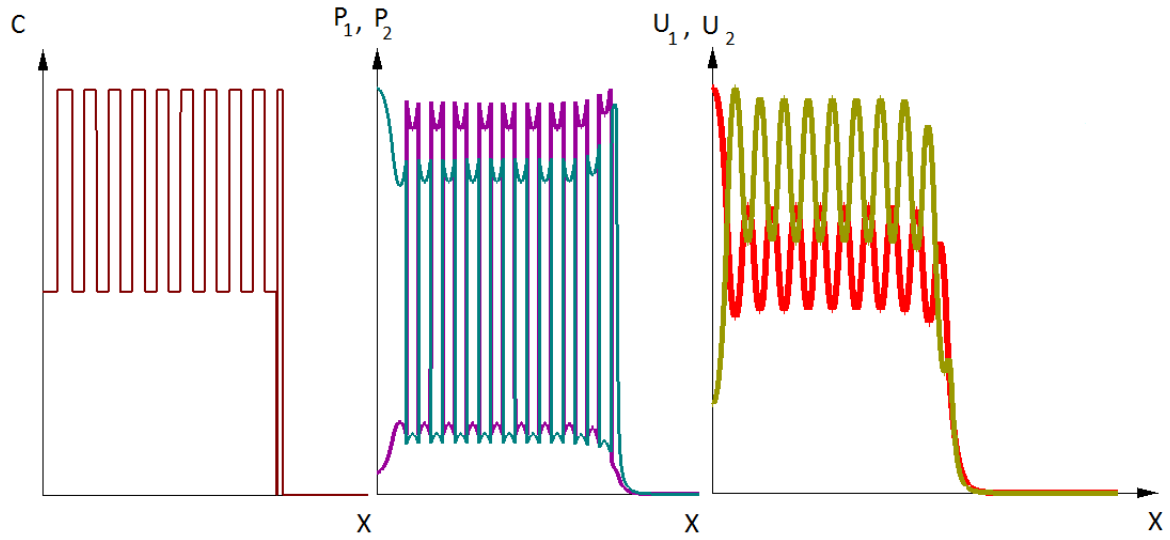

Figure 2: A snapshot of solution. The curves show the values of the corresponding concentrations as functions of the space variable x. A travelling wave of cell differentiation propagates from the left to the right. The distribution of cells B_1 ($c = 1$) and B_2 ($c = 2$) behind the wave is periodic (left image). Distributions of p_1, p_2 (middle) and of u_1, u_2 (right) oscillate in space. The value $c = 0$ corresponds to $c_A = 1, c_1 = 0, c_2 = 0$; $c = 1$ to $c_A = 0, c_1 = 1, c_2 = 0$ and $c = 2$ to $c_A = 0, c_1 = 0, c_2 = 1$. (see the explanation in the text).

Let us note that the patterns with two lineages of differentiated cells can be obtained only in the case where the stationary point P_0 of system (3.6) is stable. Otherwise, if it is unstable, then only one cell lineage will be obtained even in the case of negative feedback between cell differentiation and production of intracellular proteins. We can give the following explanation. When the two cell lineages appear, they produce the extracellular substances u_1 and u_2 which diffuse and influence undifferentiated cells where production of intracellular proteins p_1 and p_2 begins. Even if the concentrations of u_1 and u_2 are small, they are sufficient to initiate intracellular reactions since the point P_0 is unstable. Therefore

even small extracellular concentrations determine the future choice of undifferentiated cells between two cell lineages far ahead the front of differentiated cells. One of them will finally win this competition, and all differentiated cells will belong to the same type. If the point P_0 is stable, then small concentrations u_1 and u_2 will not be sufficient to start intracellular reactions. They will begin only when differentiated cells are sufficiently close. If these are cells B_1, then they will stimulate production of p_2 and vice versa. This negative feedback results in the coexistence of two cell lineages.

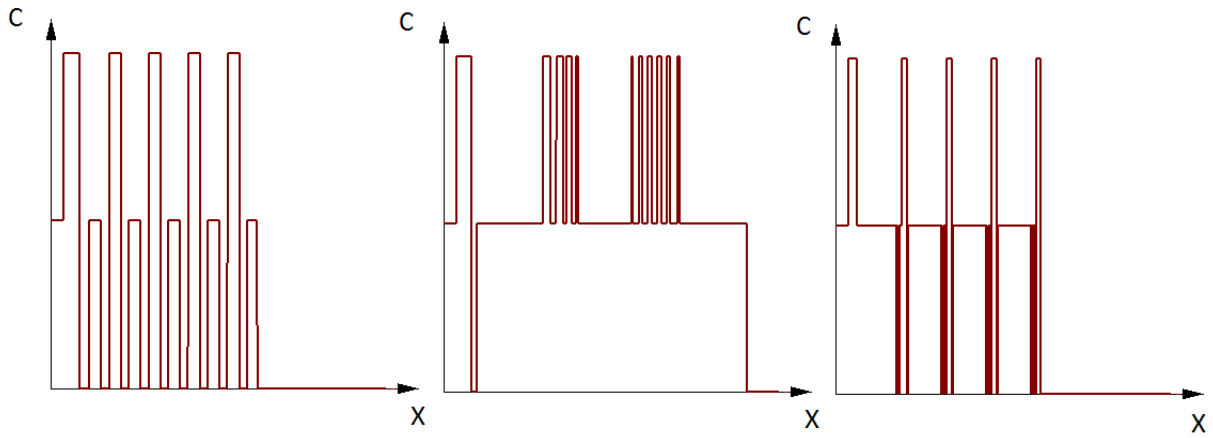

Figure 3: Distributions of differentiated cells as a function of the space variable for three different sets of parameters: $q_1 = q_2 = 0.01$ (left), $q_1 = q_2 = 0.01$, $D_2 = 0.5$ (middle), $q_1 = 0.1, q_2 = 0.01$ (right). The value $c = 0$ corresponds to $c_A = 1, c_1 = 0, c_2 = 0$; $c = 1$ to $c_A = 0, c_1 = 1, c_2 = 0$ and $c = 2$ to $c_A = 0, c_1 = 0, c_2 = 1$.

Different patterns are shown in Figure 3. Undifferentiated cells can coexist with both types of differentiated cells (left and right images) and distribution of differentiated cells can be different in comparison with the previous figure (Figure 3, middle). Figure 4 shows two different patterns of cells. In the first case, the cell concentration c takes the values $c = 1, 2, 0, 2$ in one period, while in the second case, $c = 1, 0, 2, 0, 2$.

Thus we obtain coexistence of cell lineages in the case where undifferentiated cells are stable from the point of view of intracellular regulation and where the feedback between cell differentiation and intracellular regulation is negative.

4 Discussion

The choice of cell fate between self-renewal, differentiation and apoptosis and the choice of cell lineage are determined by intracellular regulation and possibly influenced by extracellular regulation. Even if cell culture contains cells of the same type, their fate can be different. There are two possible factors which determine their choice: different cell environment (extracellular regulation) or small perturbations in the intracellular regulation. Cell

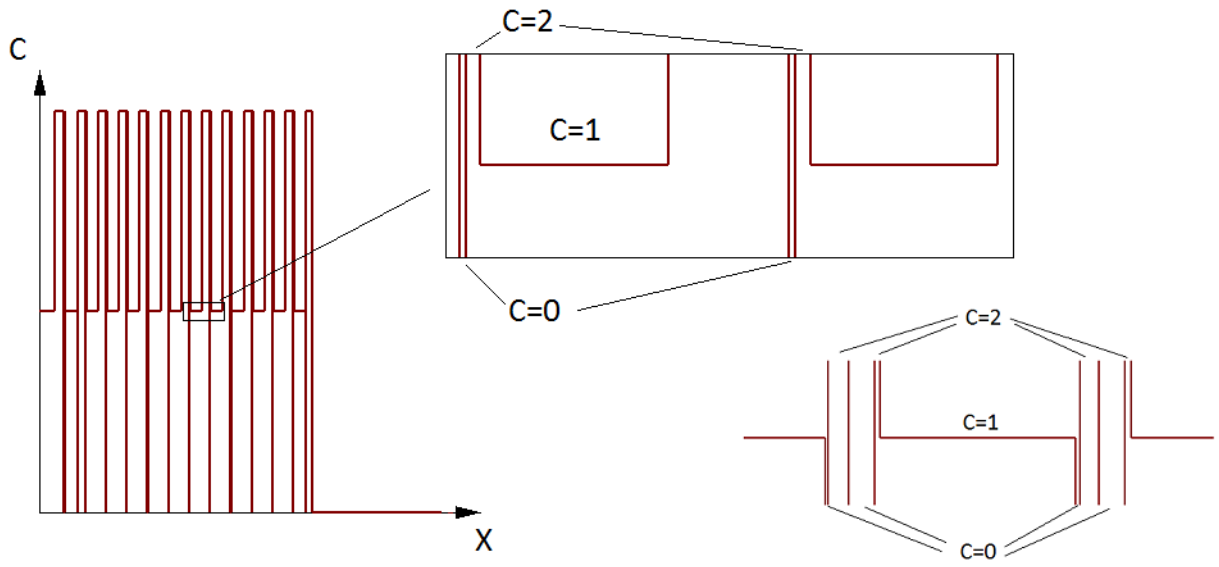

Figure 4: Periodic pattern of cell distribution behind the wave (left). Zoom on the cell concentration distribution (middle) for $s_2 = 0.15$. The pattern is different for $s_2 = 0.34$ (right). The value $c = 0$ corresponds to $c_A = 1, c_1 = 0, c_2 = 0$; $c = 1$ to $c_A = 0, c_1 = 1, c_2 = 0$ and $c = 2$ to $c_A = 0, c_1 = 0, c_2 = 1$.

environment plays a crucial role in the choice of cell fate. In particular, it is well known that stem cells can self-renew when they are located in stem cell niche, and they lose the capacity of self-renewal when they leave the niche. Let us also mention regulation of red blood cell production in erythroblastic islands in the bone marrow where macrophages control self-renewal of erythroid progenitors and Fas-ligand producing cells control their differentiation and apoptosis (Eymard et al. 2014; Fischer et al. 2012). Thus, cell-cell interaction and paracrine signaling are important for the choice of cell fate. Even if the cell population consists of cells of the same type, position of individual cells in this population is different. Mechanical stresses and density dependent proliferation can result in the difference of cell behavior, some cells can stop proliferation while some other will continue.

If cells have the same environment, then they can have different fates because of perturbations in the intracellular regulation.. Such perturbations can have different origin: small number of molecules participating in the regulation, random perturbations, hypothetical existence of mechanisms providing variations in intracellular regulation.

In this work we introduce a spatial heterogeneity in a homogeneous cell population. This perturbation initiates the wave of cell differentiation which propagates and converts undifferentiated cells into one of the lineages of differentiated cells or in both of them.

Travelling waves of cell differentiation manifest themselves in various physiological situations. In particular, they are observed in various diseases including inflammatory diseases. Cells in the inflamed part of the tissue produce proinflammatory cytokines which diffuse in

the tissue and promote inflammation of the surrounding cells. This mechanism determines growth of atherosclerotic plaques, development of the inflammation induced thrombosis (e.g., in the case of arthritis and cancer) and so on. It is also possible that development of neurodegenerative diseases is related to growth of apoptotic tissue by the same mechanism. Direct biological experiments on the propagation of cell differentiation would help to describe more precisely these mechanisms and to determine the speed of propagation (i.e., of the disease development). Medical treatment acts to decrease the speed of wave propagation. The dependence of the speed on drug concentration would be an important characteristics of its efficacy and would give some additional information about pharmacokinetics and pharmacodynamics of medical treatment.

There are different regimes of propagation of the wave of cell differentiation. I some of them we observe that two lineages of differentiated cells can coexist. Coexistence of cell lineages requires some special conditions. In order to clarify this question, consider undifferentiated cells A and two types of differentiated cells, B_1 and B_2. We can describe cell differentiation in terms of probabilities: cells A differentiate into cells B_1 with probability P_1 or in cells B_2 with probability P_2. These probabilities can be some given constants or functions of some extracellular variables (for example, u_1 and u_2, Section 3). If these probabilities are positive, then both cell lineages will always be present. However this approach implies some underlying mechanism which determines cell differentiation. In the other words, given probabilities of cell differentiation replace the mechanism of cell differentiation. Probabilistic approach is justified if we consider a small number of molecules in the intracellular regulation. However if the number of molecules participating in the intracellular regulation is sufficiently large (at least several hundred), as it is often the case, then we can introduce their concentrations and use deterministic models. In this case, conditions of cell differentiation into each of cell lineages should be also formulated deterministically. In the model considered above, we suppose that intracellular substances should reach some given critical level. If we use this approach, we do not rely on unknown mechanisms in the model. The model is completely determined. However, in this case we cannot affirm a priori that both cell lineages can coexist.

Coexistence of cell lineages is important from the physiological point of view. In hematopoiesis, production of blood cells begins with hematopoietic stem cells and leads to formation of red blood cells, platelets and several lineages of white blood cells. There are several bifurcation points where undifferentiated or partially differentiated cells make a choice between two cell lineages. So we need to understand under which conditions different cell lineages can coexist.

The results of this work show that coexistence of two cell lineages requires some particular conditions. If we have a uniform population of undifferentiated cells, and we initiate their differentiation, then usually only one cell lineage persists. Another one disappears even if both of them were initiated at the same time. In order to preserve both cell lineages we need to have stable undifferentiated cells from the point of view of intracellular regulation and negative feedback between cell differentiation and intracellular regulation.

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